REMARKS

Claims 1, 6, 7, 10, 12, 13 and 15-19 are pending in the application.

Claims 1, 6, 10, 13, 16 and 17-19 were previously presented.

Claims 7, 12 and 15 are original.

Claims 2-5, 8-9, 11 and 14 were canceled as per the previous response and were rewritten as claims 18 and 19 which now stand as previously presented.

As pointed out in the prior response, the previously presented claims 1, 6, 10, 13, 16 and 17 are intended to more accurately reflect what is applicants' invention.

The withdrawal of all the double patenting rejections is gratefully acknowledged.

Additionally, a new 37 CFR § 1.132 declaration of Stephen Michnick is enclosed that further declares that Stephen Michnick is the sole inventor of the subject matter commonly claimed between the instant application and the co-pending applications or issued patents used as the basis of outstanding rejections under 35 U.S.C. 102(f). It is believed that the new declaration now overcomes the rejections under 35 U.S.C. 102(f).

THE SPECIFICATION

The nucleotide sequences that appear in Figure 2 have now been identified as requested by the Examiner by amending the specification and the insertion of the new paragraph as shown in page 2 of this paper.

For support for the amended paragraph: see, e.g., Detailed Description of the Invention, at page 19, paragraph beginning "Figure 2 describes the steps involved in creating a PCA based on a fluorescent protein."; also the paragraph spanning pages 21-22 beginning with "Based on these criteria the optimal fragmentation regions..." in conjunction with Figure 1a, showing the alternative fragmentation sites of GFP that form the subject of the invention.

THE REJECTION UNDER 35 U.S.C. § 112

Claim 18 stands rejected under 35 U.S.C. § 112 first paragraph, as failing to comply with the enablement requirement. The Examiner quotes *In re Wands, 8 USPQ 2d 1400 (CAFC 1988)* where the CAFC considered the issue of enablement in molecular biology.

Withdrawal of this rejection is respectfully requested in view of the following remarks:

The general process of constructing a PCA is depicted in Figure 2. The present application provides over one thousand fragment compositions useful for PCA. The large number of fragments is a product of: (a) the number of different colors of starting fluorescent proteins, together with (b) the number of different fragmentation sites (6), and (c) additional point mutations which may be introduced in fragment Flor F2 and which have been shown to change the properties of the holoprotein. Thus, a large number of fragments are provided in the instant specification. Nonetheless, useful PCAs may be created without undue experimentation by following several basic steps.

The first step is to select the desired wavelength for the PCA: green, yellow, citrine, cyan,

blue, blue-green, orange or red. Once the desired color is selected, complementary fragments are selected to correspond to the full length mutant protein that fluoresces in the desired wavelength. Complementary fragments corresponding to that mutant protein will therefore generate the desired wavelength when they are caused to associate by the interacting proteins to which the fragments are fused. This initial decision, of the color of the PCA, narrows the selection of fragments to those that correspond to the starting protein that emits in the chosen wavelength.

The second step is to select a pair of fragments corresponding to one or more of the fragmentation sites shown in Fig 1. Six different fragmentation sites are shown resulting in six different F1/F2 PCA pairs for any one starting fluorescent protein. Any of the seven complementary F1/F2 pairs may be used in constructing the PCA. To obtain the optimal signal for any particular assay or protein-protein interaction, all six pairs may be tested, but often it is not necessary to test all 6 to get a positive PCA. Even with no prior knowledge of the geometry of the protein-protein interaction that is being tested, it is usually sufficient to try one or two fragmentation sites, such as those near the middle of the starting protein. If the first selection of a F1/F2 pair does not generate a signal, an alternative pair may be tried.

The order of these two steps is not critical. For example: Step 2, the selection of an optimal fragment pair, can be performed on a single fluorescent PCA (GFP or YFP) and then once a satisfactory fragment pair is found, additional assays can be created by using equivalent fragment pairs corresponding to different colors of the starting protein.

Once a positive PCA is achieved, the assay properties can often be further improved by introducing additional mutations, many of which are provided herein. The need for further improvement is determined by user preference; the particular biological or biochemical application that is needed; the cell background for the PCA; and other experimental and instrumentation variables which are well known to those skilled in the art of assay development.

In many cases, the 'starting' PCA will be sufficient for the project at hand, not requiring additional mutagenesis for signal improvement. For example, simple detection of the existence of a protein-protein interaction does not demand that the signal be optimal, only that it be detectable. On the other hand, high-throughput screening of a million-compounds library with to identify small molecule inhibitors of a particular pathway might require a highly sensitive assay capable of detecting low-level inhibition without overexpression of protein. In that case, the assay sensitivity can be enhanced until a desired sensitivity is achieved. The intensity of the signal is affected by additional mutations, which influence the fluorophore in the folded (barrel) structure of the reconstituted protein. Such additional mutations are introduced into one or both of the fragments. A finite number of such mutations are provided in Table 2 (for example: Q69M, F46L, M153T, V163A). F1/F2 fragments incorporating one or more of these well-recognized mutations are provided and claimed in the sequence listings of the instant application. The decision to introduce one or more of these mutations can be made by one skilled in the art, based on the literature references and the desired properties of the assay being constructed.

Additionally, Applicant's respectfully submit that there is sufficient guidance in pages 18-25 of the specification for how to make and use all of the claimed fragments.

DOUBLE PATENTING

Applicant acknowledges the acceptance of the two terminal disclaimers filed March 14, 2005; and further gratefully acknowledges the withdrawal of all the double patenting rejections as per pages 6 and 7 of the outstanding office action.

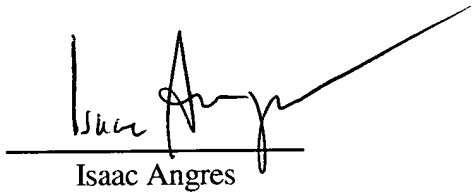
THE REJECTIONS UNDER 35 U.S.C. § 102(f)

The Examiners' attention is called to the enclosed additional declaration of Stephen Michnick under 37 C.F.R. § 1.132 which Applicant believes would now obviates the remaining rejections under rejections under 35 U.S.C § 102(f). The new declaration now states (see paragraph No. 3) that Stephen Michnick is the sole inventor of the subject matter commonly claimed between the instant application and the co-pending applications or issued patents upon which the rejection is based.

In view of the above amendments and remarks, it is respectfully submitted that the claims are now in condition for allowance. The Examiner is invited to contact the undersigned at 703-418-2777 if he feels that further discussion may facilitate the resolution of any outstanding issues.

An early indication of a Notice of Allowance is earnestly solicited.

Respectfully submitted,



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